

US EPA ARCHIVE DOCUMENT

EPA-HSRB-09-10

Kevin P. Teichman, PhD
Acting Science Advisor
Office of the Science Advisor
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: October 20-21, 2009 EPA Human Studies Review Board Meeting Report

Dear Dr. Teichman,

The United States Environmental Protection Agency (EPA or Agency) requested the Human Studies Review Board (HSRB) to review two completed intentional studies examining the effects of intentional exposure of human participants to pesticides containing pyrethrins/pyrethroids. The Agency proposes to rely on these two studies, conducted prior to publication of the EPA's expanded final rule for protection of subjects in human research (40 CFR 26) on February 6, 2006 (71 Federal Register 24, 6137), for regulatory actions under the pesticide laws. The Agency asked the HSRB to advise the Agency on a range of scientific and ethics issues regarding how the studies should be assessed against the provisions in 40 CFR sections 26.1701 – 26.1704 of the final human studies rule.

The Agency also requested the HSRB to provide scientific and ethics reviews of two proposed human studies: a proposed Carroll-Loye Biological Research, Inc. (CLBR) insect repellent efficacy study (LNX-003); and a proposed Antimicrobial Exposure Assessment Task Force II (AEATF II) aerosol spray application protocol (AEA04).

The enclosed report provides the Board's response to EPA charge questions presented at the October 20-21, 2009 meeting.

Assessment of Completed Research Study: Newton, J., Breslin, A. (1983) Asthmatic reactions to a commonly used aerosol insect killer. *Medical Journal of Australia* 1:378-380.

Science

- Because of the complex nature of the insecticide product that was evaluated, the Board concluded that the Newton and Breslin study was not relevant when considering the asthmatic or allergic respiratory response for pyrethrins/pyrethroids as a class. The Newton and Breslin study was relevant when considering the asthmatic or allergic respiratory response only for the specific insecticide product that was tested.
- Considering the substantial limitations of the study, the Board concluded that the study was of limited utility. The Board recommended that the Agency be cautious in its use of these data, limiting it to a qualitative contribution to the overall weight of evidence.

Ethics

- Given the limited information available about this study, the Board concluded that there neither was clear and convincing evidence that the study was fundamentally unethical, nor clear and convincing evidence that the study was significantly deficient relative to the ethical standards prevailing at the time the research was conducted.

Assessment of Completed Research Study: Lisi, P. (1992) Short Communication: Sensitization risk of pyrethroid insecticides. *Contact Dermatitis* 26:349-350.

Science

- The Board concluded that the Lisi study was likely sound, but the brevity of the report and limited details as to how the study was conducted prevent an accurate assessment of its reliability.
- If carried out according to accepted guidelines and criteria, the Lisi study likely provides hazard assessment data that are relevant to assessing whether exposures to pyrethrins/pyrethroids may be associated with allergic contact dermatitis or sensitization responses.
- Although the data presented in the Lisi study suggest that the seven compounds tested pose little risk of allergic contact dermatitis or skin sensitization, unanswered questions about participant history and selection, study procedures, and outcome definitions should be taken into account when considering these data in the overall analysis.

Ethics

- Given the limited information available about this study, the Board concluded that there neither was clear and convincing evidence that the study was fundamentally unethical, nor clear and convincing evidence that the study was significantly deficient relative to the ethical standards prevailing at the time the research was conducted.

Assessment of Proposed Carroll-Love Biological Research Study LNX-003: Efficacy Test of KBR 3023 (Picaridin; Icaridin) - Based Personal Insect Repellents (20% Cream and 20% Spray) with Ticks Under Laboratory Conditions.

Science

- The Board concluded that the protocol submitted for review, if modified in accordance with Agency recommendations and conducted accordingly, will likely yield scientifically valid results on the efficacy of these two picaridin-based insect repellent formulations against ticks.

Ethics

- The Board concluded that the protocol submitted for review, if modified in accordance with Agency recommendations and conducted accordingly, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L.

Assessment of Proposed AEATF II Scenario and Protocol AEA04: Research on Exposure of Janitorial Works Applying Pesticides Formulated as Aerosol Sprays.

Science

- The Board concluded that the protocol submitted for review, if modified in accordance with Agency and HSRB recommendations, will likely generate scientifically reliable data, useful for assessing the exposure of handlers who apply antimicrobial pesticides formulated as aerosol sprays.
- The Board provided a number of recommendations for how the study could be improved, including: clarifying the criteria for exclusion of participants who deviate grossly from the protocol; acknowledging that systematic differences in the air sampling results are likely to occur between the two methods used; and, considering carefully other variables that may influence exposure measurements.

Ethics

- The Board concluded that the protocol submitted for review, if modified in accordance with Agency and HSRB recommendations and conducted accordingly, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L.
- The Board recommended that the protocol be revised to address certain concerns, including: ensuring that documents in Spanish are reviewed by someone familiar with the dialect written and spoken in the target community; design and posting of community notification flyers appropriate for guests staying at the motels where study procedures are likely to take place; and, exclusion of volunteers who may be at greater risk of product-related harm due to immunodeficiency or other underlying conditions.

Sincerely,



Sean Philpott, PhD, MSBioethics
Chair
EPA Human Studies Review Board

NOTICE

This report has been written as part of the activities of the EPA Human Studies Review Board, a Federal advisory committee providing advice, information and recommendations on issues related to scientific and ethical aspects of human subjects research. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the view and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does the mention of trade names or commercial products constitute a recommendation for use. You may obtain further information about the EPA Human Studies Review Board from its website at <http://www.epa.gov/osa/hsrb>. You may also contact the HSRB Designated Federal Officer, via e-mail at phre@epa.gov

In preparing this document, the Board carefully considered all information provided and presented by the Agency presenters, as well as information presented by public commenters. This document addresses the information provided and presented within the structure of the charge by the Agency.

**US ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD**

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Proposed Final Draft Dated November 29, 2009; Do Not Cite or Quote

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* Not in attendance at October 20-21, 2009 Public Meeting

INTRODUCTION

From October 20-21, 2009, the United States Environmental Protection Agency's (EPA or Agency) Human Studies Review Board (HSRB) met to address scientific and ethical issues concerning: two completed human toxicity studies involving one class of pesticide active ingredients – pyrethrins/pyrethroids– conducted prior to publication of the EPA's expanded final rule for protection of subjects in human research. In accordance with 40 CFR 26.1602, EPA sought HSRB review of these completed studies. Each of these completed studies is discussed more fully below.

In addition, the Agency submitted two protocols for conducting new research involving human participants: one study measuring the efficacy of two registered insect repellents containing picaridin against ticks under laboratory conditions; and one study measuring levels of exposure received by janitorial workers when applying a commercially-available antimicrobial pesticide formulated as an aerosol spray. In accordance with 40 CFR 26.1601, EPA sought HSRB review of these two proposed protocols. Each of these protocols is discussed more fully below.

REVIEW PROCESS

On October 20-21, 2009, the Board conducted a public face-to-face meeting in Arlington, Virginia. Advance notice of the meeting was published in the Federal Register as "Human Studies Review Board; Notice of Public Meeting" (74 Federal Register 106, 26861).

Following welcoming remarks from Agency officials, the Board heard presentations from EPA on the following topics: two completed studies involving intentional human exposure to pyrethrin/pyrethroid pesticides (Newton and Breslin [1983], and Lisi [1992]); a proposed Carroll-Loye Biological Research, Inc. (CLBR) insect repellent efficacy study (LNX-003); and a proposed Antimicrobial Exposure Assessment Task Force II (AEATF II) aerosol spray application protocol (AEA04).

The Board also asked clarifying questions of several study sponsors and/or research investigators, including:

Dr. Scott Carroll, Principal, Carroll-Loye Biological Research
Dr. Jeffery Driver, Principal, infoscientific.com, Inc.
Mr. Shawn King, Director of Operations, Carroll-Loye Biological Research
Dr. Bryce Landenberger, Dow AgroSciences
Dr. Sami Selim, President, Golden Pacific Laboratories

Oral comments were provided by:

Dr. Scott Carroll, Principal, Carroll-Loye Biological Research

Mr. Stephen McFadden, Independent Advocate
Dr. Lawrence Plumlee, Independent Advocate

No written public comments were provided.

For their deliberations, the Board considered the materials presented at the meeting, oral comments, and Agency background documents (e.g., published literature, sponsor and investigator research reports, study protocols, data evaluation records, and Agency science and ethics reviews of proposed protocols and completed studies). A comprehensive list of background documents is available online at <http://www.regulations.gov>.

CHARGE TO THE BOARD AND BOARD RESPONSE

Assessment of Completed Research Study: Newton, J., Breslin, A. (1983) Asthmatic reactions to a commonly used aerosol insect killer. *Medical Journal of Australia* 1:378-380.

Overview of the Study

In the Newton and Breslin (1982) study, seven participants diagnosed with asthma and a history of chest tightness were evaluated for airway narrowing and chest tightening before and after a controlled exposure to aerosol insecticide sprays. Participants were exposed to a commercially-available aerosol insecticide (Mortein Pressure Pak insect killer containing 3.0 g/kg pyrethrins, 0.9 g/kg tetramethrin, 15 g/kg piperonyl butoxide, 7.5 g/kg N-octyl-bicycloheptene dicarbonyls, propellants [chlorofluorocarbons and hydrocarbons] and solvents [non-water based]). The aim of the study was three-fold: to study the response of asthmatic participants to exposure to insecticides containing pyrethrins and tetramethrin; to study the time-course of exacerbation of asthma following exposure to the insecticide; and to evaluate bronchial reactivity to histamine after exposure to the insecticide. Data were reported as simple counts or proportions across exposure groups.

Science

Charge to the Board

Is the Newton and Breslin (1983) study scientifically sound, providing reliable data?

Board Response to the Charge

In light of the substantial limitations of the study, the Board concluded that the study was of limited utility. The Board recommended that the Agency be cautious in its use of these data, limiting it to a qualitative contribution to the overall weight of evidence. The use of these data should also be limited to assessments of the specific insecticide product tested rather than pyrethrins/pyrethroids as a class of pesticides.

Charge to the Board

Is the Newton and Breslin (1983) study relevant to an assessment of the proposition that exposures to pyrethrins/pyrethroids may be associated with asthmatic or allergic respiratory responses?

Board Response to the Charge

The Board concluded that the Newton and Breslin study was relevant only when considering the asthmatic or allergic respiratory response for the specific insecticide product that was tested. It was not relevant when considering the asthmatic or allergic respiratory response for pyrethrins/pyrethroids as a class because of the complex nature of the insecticide product that was evaluated.

Charge to the Board

What limitations of the Newton and Breslin (1983) study should be taken into account by EPA in assessing the proposition that exposures to pyrethrins/pyrethroids may be associated with asthmatic or allergic respiratory responses?

Board Response to the Charge

The Board cautioned against using the Newton and Breslin study for assessing the proposition that exposures to pyrethrins/pyrethroids may be associated with asthmatic or allergic respiratory responses. The use of a complex insecticide product rather than a specific chemical was of considerable concern, as was the more robust response for respiratory irritation rather than asthma or allergy reported in the study.

HSRB Detailed Recommendations and Rationale

The Newton and Breslin (1982) article provided an incomplete record of the conduct of the study and analysis of the data, such that a number of important data gaps were identified.

One primary concern was that the tested material contained a mixture of ingredients, some of those ingredients at higher concentrations than the pyrethrins. One such ingredient, piperonyl butoxide, has been identified previously as a potential respiratory allergen (EPA Office of Pesticide Programs 2009). Accordingly, the Board concluded that the data obtained by Newton and Breslin are directly applicable only to the product tested, and are not broadly applicable to pyrethrins/pyrethroids as a pesticide class.

Other major issues and limitations noted during the Board's discussion included:

1. *Limited and likely inaccurate exposure data.*
 - a. Exposures to the test material were not directly measured, but were calculated based on the assessment of the amount of product delivered per unit time. Study participants were

likely to have been exposed to the experimental product, but the lack of data on the actual exposure rate or concentration precludes any quantitative evaluation.

- b. The Newton and Breslin article provides a description that is inadequate to assess whether the facility was appropriate for this type of testing. The test chamber was described as a 7-m³ room with large windows on one side for observation purposes and an exhaust fan that “removed fumes between sprays.” There is no indication, however, that there was a standardized protocol that governed spraying procedures or cleaning requirements between exposures. There also was no indication whether the air exchange rate of the room or cleaning procedures between exposures were sufficient to ensure that the exposure levels intended by the investigators were delivered. Thus, there may be a high degree of error in the estimated exposures, as compared to the actual exposures.
 - c. There was no mention of factors that may have affected actual exposures, such as the distance between participant and spray nozzle, spray droplet size, or any odorants or deodorants used to “mask” the product spray from the placebo.
2. *Small sample size.*
 - a. Although study subjects were noted to have a predisposition for asthma, and thus likely to be potentially susceptible to showing an effect, only seven participants were evaluated.
 - b. There is insufficient descriptive information for the seven participants chosen, such as parameters of respiratory function and disease state. It was also noted that the two oldest participants were both male, but no consideration whether age, gender or other participant characteristics may have affected the study results.
 3. *Incomplete results and data analysis.*
 - a. Two subjects did not complete the pretest histamine challenge, and three subjects did not complete the post-exposure challenge. Maximum mid-expiratory flow rate (MMEFR) was not measured for one subject. More notable is the fact that the only subject with a significant decrease in forced expiratory volume in one second (FEV1) did not complete either histamine challenge evaluation. No explanation for participants’ failure to complete these study procedures and tests was provided.
 - b. There are limited details on how FEV1 and MMEFR values were reported. It was noted during the Board’s discussion that standard clinical practice is to report the maximum values, but it is unclear if this was done in the Newton and Breslin study.
 - c. There was no indication that baseline FEV1 or MMEFR values were within the normal ranges for these participants, nor any additional detail on participant characteristics that could affect these values, such as age, gender, body size, or underlying disease.

- d. There was no specific designation of the symptoms that each patient experienced. It is not clear which patient was the person not counted among the “6 of 7” who experienced chest tightness with other symptoms.
- e. There was no specific indication whether and how the observation of respiratory irritation correlated with changes in FEV or MMEFR values.
- f. It is unclear which participants were tested at which levels of exposure (e.g. 10 versus 20 seconds), how many times each person was exposed at each exposure duration, or which volunteers received the placebo on day 2.

4. *Potential information bias.*

- a. Participants were not blinded to treatment, and there was no description of how symptoms were self-diagnosed and reported by volunteers. Without the use of standardized definitions as a reference, there is no way to know whether each participant had the same interpretation and reporting practices for self-diagnosed respiratory symptoms.

Ethics

Charge to the Board

Is there clear and convincing evidence that the conduct of the Newton and Breslin (1983) study was fundamentally unethical, or significantly deficient relative to the standards of ethical research conduct prevailing when it was conducted?

Board Response to the Charge

Given the limited information available about this study, the Board concurred with the Agency’s assessment (Sherman 2009a) that there neither was clear and convincing evidence that the study was fundamentally unethical, nor clear and convincing evidence that the study was significantly deficient relative to the ethical standards prevailing at the time the research was conducted.

HSRB Detailed Recommendations and Rationale

The Newton and Breslin study was conducted in Australia in 1981 or 1982. The Board concurred with the Agency’s assessment that most widely recognized ethical standard at that time was the 1975 Declaration of Helsinki, but also noted the importance of placing ethical standards within a specific national context. The Australian National Health and Medical Research Council (NHMRC) -- the largest public supporter of research in Australia -- issued guidelines as early as 1966 that requiring all NHMRC-funded research to be reviewed by an independent ethics committee. A 1976 supplementary note to these guidelines, prompted by and explicitly referencing the Declaration of Helsinki, called upon all Australian research facilities to establish committees to review all research involving human participants, NHMRC-funded or otherwise.

Limited information is available about how the Newton and Breslin study was conducted. The Agency attempted to obtain additional information about the conduct of this study, but was unable to do so. The only available information is from the published article, which states that the written informed consent of all participants was obtained. The article also indicates that all participants were adults, and that none of the female volunteers were pregnant. Although the article does not describe the type of ethical oversight of this research that took place, it is assumed that independent ethics review occurred in accordance with NHMRC guidelines.

Considering the information available, the Board concurred with the conclusions and factual observations of the ethical strengths and weaknesses of the study, as detailed in the Agency's Ethics Review (Sherman 2009a). The Board also concluded that this study met all applicable ethical requirements for such research involving human participants, as required by the Final Human Studies Rule, according to the following criteria:

- a. *Not fundamentally unethical.* When determining whether or not a study is fundamentally unethical, the Board's standard approach is to decide if the research was intended to seriously harm participants, if it failed to obtain informed consent, or if it was fundamentally unethical for other reasons. In this case, there was no evidence that the study was intended to seriously harm participants. The published article also failed to provide evidence supporting a conclusion that the informed consent of participants was not obtained. Given lack of clear and convincing evidence that for any other reasons it might have been fundamentally unethical, the Board concluded that it was not fundamentally unethical.
- b. *Not significantly deficient.* With regard to determining whether a study was significantly deficient relative to the ethical standards prevailing at the time the research was conducted, the Board's standard is to determine whether or not any ethical deficiencies identified could have resulted in serious harm to participants, based on knowledge available to researchers at the time the study was conducted, or whether the information provided to study participants could seriously impair informed consent. As noted above, there is limited information available regarding this study. Only the published article provides any information, and the information contained therein fails to support a conclusion that the study was significantly deficient relative to the standards at the time.

Assessment of Completed Research Study: Lisi, P. (1992) Short Communication: Sensitization risk of pyrethroid insecticides. *Contact Dermatitis* 26:349-350.

Overview of the Study

In the Lisi (1992) study, 230 volunteers were patch tested with each of seven pyrethroids: allethrin, cypermethrin, deltamethrin, fenothrin (assumed phenothrin), fenvalerate, permethrin, resmethrin. The goal was to establish the irritation and sensitization potential of these widely used pyrethroids. Of the volunteers who participated, 162 were men and 68 were women. Participants ranged from 19 to 78 years

in age. Approximately 35% of participants were agricultural workers, 12% had previously worked on a farm, and the remaining 53% were engaged in nonagricultural activities. Fifty-four subjects had irritant or allergic contact dermatitis of the hands, 18 of which were correlated with agricultural activities. A further 176 participants had non-allergic skin disorders, and 16 participants were also atopic. Simple counts and proportions were used to compare irritation and sensitization effects across the three occupational groups.

Science

Charge to the Board

Is the Lisi (1992) study scientifically sound, providing reliable data?

Board Response to the Charge

The Board concluded that the Lisi study was likely sound, but the brevity of the report and limited details as to how the study was conducted prevent an accurate assessment of its reliability.

Charge to the Board

Is the Lisi (1992) study relevant to an assessment of the proposition that exposures to pyrethrins/pyrethroids may be associated with allergic contact dermatitis or sensitization responses?

Board Response to the Charge

If the Lisi study was carried out according to accepted guidelines and criteria, it likely provides hazard assessment data that are relevant to assessing whether exposures to pyrethrins/pyrethroids may be associated with allergic contact dermatitis or sensitization responses.

Charge to the Board

What limitations of the Lisi (1992) study should be taken into account by EPA in assessing the proposition that exposures to pyrethrins/pyrethroids may be associated with allergic contact dermatitis or sensitization responses?

Board Response to the Charge

A lack of experimental detail and subject history represent two major limitations of the Lisi study. The Board also noted that the allergic/irritant response rate was extremely low in the study. This may suggest that the seven compounds tested pose little risk of allergic contact dermatitis or skin sensitization but the low response rate, along with concerns about participant

history and selection, study procedures, and outcome definitions, should be taken into account when considering these data in the overall weight-of-evidence analysis.

HSRB Detailed Recommendations and Rationale

The extremely brief nature of the report raised a number of questions about how the study was conducted. Because the study was reportedly performed according to standards and criteria established by the International Contact Dermatitis Research Group (ICDRG), the Board assumed that standard testing procedures were used.

Major issues and limitations noted during the Board's discussion included:

1. *Poorly defined participant population.*
 - a. It was unclear how the 230 participants were chosen for study.
 - b. Subjects were identified as "agricultural workers," "ex-agricultural workers," or "other," but there was no explanation for creating and using these categories.
 - c. Participant compliance with study procedures was not reported. There was no indication as whether any participants withdrew or were otherwise not observed, nor did the report provide any detail whether all test patches were evaluated for all participants on days 2 and 3.
2. *Lack of protocol detail.*
 - a. ICDRG protocols may have been used, but the report provides few details on how investigators distinguished allergic versus irritant responses or any information on how they graded response severity.
3. *Low response rate.*
 - a. The low response rate (less than 2% of all study participants) suggests that the seven compounds tested pose little risk of allergic contact dermatitis or skin sensitization. However, these data could also be indicative of problems in study design and conduct that invalidate the results. Because the appropriate positive and negative controls were not included in the study design, the Board felt that it could not rule out this alternative explanation for the low response rate.

Ethics

Charge to the Board

Is there clear and convincing evidence that the conduct of the Lisi (1992) study was fundamentally unethical, or significantly deficient relative to the standards of ethical research conduct prevailing when it was conducted?

Board Response to the Charge

Given the extremely limited information available about this study, the Board concurred with the Agency's assessment (Sherman 2009b) that there was neither clear and convincing evidence that the study was fundamentally unethical, nor clear and convincing evidence that the study was significantly deficient relative to the ethical standards prevailing at the time the research was conducted.

HSRB Detailed Recommendations and Rationale

The Lisi study was conducted in Italy sometime in 1990 or 1991. The Board concurred with the Agency's assessment that the most widely recognized ethical standard at that time was the 1989 Declaration of Helsinki, but again noted the importance of placing ethical standards within a specific national context. Italy had established a National Bioethics Committee in 1990. That Committee may have developed directives applicable to this study. Nevertheless, as explained below, the potential existence of those national standards does not alter the Board analysis.

Extremely limited information is available about how the Lisi study was conducted. The EPA attempted to obtain additional information about the design and conduct of the study, but was unable to do so. The only available information is from the published article, which does not state whether written informed consent of the participants was obtained. The published article also does not address what type of ethical oversight took place (e.g. review by an independent ethics committee). Study participants were reported to be adults, and there is no indication that any of the participants were pregnant or nursing. Although the EPA ethics review states that "there is no evidence suggesting that any subjects came from an especially vulnerable group," several of participants were current and former agricultural workers. Such participants may be socioeconomically or educationally disadvantaged, and thus may be vulnerable. The Board recommended that the Agency more clearly articulate or standardize its definition of vulnerability.

Considering the information available, the Board concurred with the conclusions and factual observations of the ethical strengths and weaknesses of the study, as detailed in the Agency's Ethics Review (Sherman 2009b). The Board also concluded that this study met all applicable ethical requirements for such research involving human participants, as required by the Final Human Studies Rule, according to the following criteria:

- a. *Not fundamentally unethical.* When determining whether or not a study is fundamentally unethical, the Board's standard approach is to decide if the research was intended to seriously harm participants, if it failed to obtain informed consent, or if it was fundamentally unethical for other reasons. In this case, there was no evidence that the study was intended to seriously harm participants. The published article also failed to provide evidence supporting a conclusion that the informed consent of participants was not obtained. Given the lack of clear and convincing evidence that for any other reasons it might have been fundamentally unethical, the Board concluded that it was not fundamentally unethical.

- b. *Not significantly deficient.* With regard to determining whether a study was significantly deficient relative to the ethical standards prevailing at the time the research was conducted, the Board's standard is to determine whether or not any ethical deficiencies identified could have resulted in serious harm to participants, based on knowledge available to researchers at the time the study was conducted, or whether the information provided to study participants could seriously impair informed consent. Only the published article provides any information, and the information contained therein fails to support a conclusion that the study was significantly deficient relative to the standards at the time.

Assessment of Proposed Carroll-Loye Biological Research Study LNX-003: Efficacy Test of KBR 3023 (Picaridin; Icaridin) - Based Personal Insect Repellents (20% Cream and 20% Spray) with Ticks Under Laboratory Conditions.

Overview of the Study

The protocol describes a study to measure the effectiveness of picaridin as a tick repellent when used in one of two compound formulations (20% picaridin KBR 3032 All-Family Insect Repellent Cream and 20% picaridin KBR 3023 All-Family Insect Repellent Spray). Dosimetry data accumulated in previous Carroll-Loye studies (LNX-001 and LNX-002) would be used for dose selection. The efficacy of picaridin as a tick repellent will be determined in a controlled laboratory setting by placing both Western black-legged ticks (*Ixodes pacificus*) and American dog ticks (*Dermacentor variabilis*) on picaridin-treated and untreated forearms and measuring the speed and distance that moving ticks would penetrate into the treated area at 15-minute intervals. A total of 40 participants will be enrolled.

Science

Charge to the Board

If the proposed laboratory tick repellency study protocol LNX-003 is revised as suggested in EPA's review and if the research is performed as described, is the research likely to generate scientifically reliable data, useful for assessing the efficacy of the tested materials in repelling ticks?

Board Response to the Charge

The Board concluded that the protocol submitted for review, if modified in accordance with Agency recommendations and conducted accordingly, will likely yield scientifically valid results on the efficacy of these two picaridin-based insect repellent formulations against ticks.

HSRB Detailed Recommendations and Rationale

Protocol LNX-003 from Carroll-Loye Biological Research (Carroll 2009a, 2009b) will be conducted using methods similar to those presented to and commented on by the Board in the

past. Although the study protocol was overly long and includes redundant or unnecessary text, it was relatively clear and addressed adequately a number of key scientific issues, including: scientific justification, objectives, and data collection and compilation methods.

The proposed methods largely follow EPA's guidelines, with the one notable exception being the use of ten volunteers per study aim, rather than the Agency's existing recommendation of six volunteers per study aim. The greater number of study participants should yield more useful information than might otherwise be obtained. The protocol also incorporated a number of recommendations that had been made by the Board previously, such as the use of dosimetry-generated data rather than use of a standardized dosage amount, which will likely generate data more representative of real-world use by consumers.

As has been pointed out previously in Board reviews of other repellency protocols, the proposed statistical approach is not ideal and the calculation of complete protection time is not the best end-use of the study data. Calculating the proportion of individuals protected for a given time may be a better way to report the data and should be considered.

Ethics

Charge to the Board

If the proposed laboratory tick repellency study protocol LNX-003 is revised as suggested in EPA's review and if the research is performed as described, is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

Board Response to the Charge

The Board concluded that the proposed laboratory tick repellency study protocol LNX-003, if modified in accordance with EPA (Sherman and Sweeney 2009) recommendations, and performed as described, will likely meet the applicable requirements of 40 CFR 26, subparts K and L.

HSRB Detailed Recommendations and Rationale

The submitted documents assert that the study will be conducted in accordance with the ethical and regulatory standards of 40 CFR 26, Subparts K and L, as well as the requirements the US EPA's GLP Standards described at 40 CFR 160, and the California State EPA Department of Pesticide Regulation study monitoring (California Code of Regulations Title 3, Section 6710) (Carroll 2009a, 2009b). Requirements of FIFRA §12(a)(2)(P) also apply. The protocol was reviewed and approved by an independent human subjects review committee, Independent Investigational Review Board, Inc. (IIRB, Inc.), of Plantation, FL, prior to submission. Minutes of IIRB, Inc. meetings and a copy of IIRB, Inc. policies and procedures were provided to the EPA as a separate document (IIRB, Inc. 2009). These documents indicate that IIRB, Inc. reviewed this protocol pursuant to the standards of the Common Rule (45 CFR Part 46, Subpart A).

1. The Board concurred with the conclusions and factual observations of the ethical strengths and weaknesses of the study, as detailed in the EPA's Ethics Review (Sherman and Sweeney 2009). The proposed study is likely to meet the applicable ethical requirements for research involving human participants, in accordance with the following criteria:
 - a. *Acceptable risk-benefit ratio.* The risks as noted in the study protocol are fivefold: 1) allergic reaction to test materials themselves; 2) exposure to biting arthropods; 3) possible exposure to arthropod-borne diseases; 4) physical stress from the test conditions; and 5) psychological stress and/or breach of confidentiality for pregnancy test results. These risks are minimized appropriately and are justified by the potential societal benefits, particularly data on the efficacy of these new formulations as personal insect repellents.
 - Based on toxicological data currently available for picaridin, coupled with appropriate exclusion criteria, study participants are unlikely to be at risk of adverse side effects with exposure.
 - The risk of bites is negligible and minimized by the study design; tick questing and biting behavior is slow, and study participants are trained to remove ticks from their forearms prior to biting. Study participants will be trained in proper insect observation and handling techniques.
 - The ticks used for the study are bred and raised in a laboratory environment and are considered to be pathogen-free, minimizing the risk of vector-borne disease. Tick colonies and their rabbit hosts are also screened regularly for known tick-borne diseases, including the rickettsial illness Rocky Mountain Spotted Fever that has been observed in the past to be transmitted within laboratory tick colonies through a trans-ovarian mechanism.
 - The potential risks to participants from physical stress are minimized. Although the 12-hour duration of the study protocol raises some concerns about physical stress and exhaustion, the study investigators attest that similar protocols of equivalent length have never been seen as unduly stressful by study participants. Appropriate stopping rules and medical management procedures are in place. Participants are also given frequent breaks and can withdraw from the study at any time should the investigational procedures prove too strenuous.
 - Minors and pregnant or lactating women are excluded from participation, with pregnancy either confirmed by over-the-counter pregnancy testing on the day of study or by opt-out. The potential stigma resulting from study exclusion due to pregnancy is also appropriately minimized.
 - b. *Voluntary and informed consent of all participants*
 - The study protocol includes several mechanisms designed to minimize coercive recruitment and enrollment. For example, although many of the research participants will be recruited from the University of California at Davis student population, where

Dr. Carroll holds an adjunct appointment, student and employees of the Study Directory are excluded from participation. Additional mechanisms design to minimize coercive recruitment, developed in response to earlier HSRB concerns and recommendations (c.f. EPA HSRB 2006a; 2006b) are also in place.

- Monetary compensation is not so high as to unduly influence participants.

c. *Equitable selection of study participants*

- The majority of research participants will be recruited from the University of California at Davis student population. Study participants are likely to reflect the ethnic and racial diversity of individuals in the City of Davis, but the use of this convenience sample may limit the broad applicability of the study results to the general population. The investigators have noted this fact in the protocol.

Assessment of Proposed AEATF II Scenario and Protocol AEA04: Research on Exposure of Janitorial Workers Applying Pesticides Formulated as Aerosol Sprays.

Overview of the Study

AEATF II aerosol spraying scenario is designed to measure a typical occupational handler's daily exposure to an antimicrobial spray packaged in a pressurized aerosol spray can. These data will be used generically to estimate dermal and inhalation exposures and risks for other antimicrobial ingredients where the product is packaged in a pressurized aerosol spray can. The Task Force expects these data to be useful for estimating exposures for various types of aerosol spray products, different types of surfaces, different room configurations, different types of buildings, different handlers, and various antimicrobial active ingredients. Eighteen professional janitors will be enrolled in the study, and asked to apply (spray but not wipe) the product at one of three motels in the Fresno, CA area. Study participants will be randomized to apply different amounts of product, from 1 to 4 cans of product in 1/2-can increments (i.e., 1 to 1.5 cans, 1.5 to 2 cans, up to 3.5 to 4 cans). Dermal and inhalation exposure will be measured using whole-body dosimeters (inner and outer), hand and face washes, and personal air monitors.

Science

Charge to the Board

If the proposed AEATF II aerosol application scenario and field study protocol AEA04 is revised as suggested in EPA's review and if the research is performed as described, is the research likely to generate scientifically reliable data, useful for assessing the exposure of handlers who apply antimicrobial pesticides formulated as aerosol sprays?

Board Response to the Charge

The Board concluded that this protocol, if modified in accordance with EPA (Leighton, Walls and Sherman 2009) and HSRB recommendations, will likely generate scientifically reliable data, useful for assessing the exposure of handlers who apply antimicrobial pesticides formulated as aerosol sprays.

The Board also recommended a number of protocol modifications, as listed below. Additional Board review of the protocol is not required prior to study implementation.

HSRB Detailed Recommendations and Rationale

The Board concluded that the protocol (AEATF II 2009a, 2009b) and supplemental SOPs (AEATF II 2009b) address adequately a number of key scientific issues, including: scientific objective, quantification of the test materials, data collection and compilation methods and summary of test results, justification for selection of the test substances, and QA/QC requirements. The process used to select the product to be tested seems rational. The AEATF II has described in detail their sampling design for the aerosol scenario, and has incorporated random elements where feasible. The aerosol scenario is well defined, and the diversity of daily exposures under the aerosol scenario as defined in this proposal is likely to describe adequately a typical occupational handler's daily exposure to this antimicrobial application. The environmental monitoring, exposure monitoring and analytic techniques appear to be adequate. The variation in exposure should be sufficient to determine a distribution of exposures.

The Board did raise a number of concerns about perceived inadequacies in the study design, as summarized below:

1. *Use of the results:* The EPA's Antimicrobials Division (AD) plans to use the data generated from the proposed aerosol study generically to estimate dermal and inhalation exposures and risks for other antimicrobial ingredients where the product is packaged in a pressurized aerosol spray can. However, other variables can affect rates of exposure, including different nozzle sizes, spray and ejection rates, the size of the particles generated, and the generation of nonvolatile active ingredients. Inhalation versus dermal exposure may also vary with these variables.

It is also unclear if occupational handler exposure can be used to estimate exposures of nonprofessionals using similar consumer products. However, for risk assessment purposes it was felt that exposure among occupational users is likely to exceed that of consumers; the higher frequency of exposures among occupational users is likely to exceed a plausibly higher individual but less frequent exposure among nonprofessional users.

2. *Sample Size & Analysis:* Raw and descriptive data will be provided, but no statistical analyses have been planned. Based on the information provided, a sample size of 18 participants may be sufficient. Placing these 18 participants into three clusters of six each requires consideration of cluster effects as well, and may complicate analysis of the results.

Assumed constants related to exposure to the active ingredient may also prove to be incorrect, and additional study participants may need to be enrolled.

3. *Application of spray*: The target number of cans sprayed in each location by each worker on each day could be specified better within the protocol. For example, does a worker need to continue spraying a room if the target application is met before completion of that room? Additional protocol clarifications needed include: addressing the issue of the interval between sampling at different sites (currently, it appears that no two monitoring events can occur within the same building within one week); clarifying the issue of using empty apartments rather than motel rooms; and clarifying the effect of exhaust vent effects on exposure, which could be different than indicated in the protocol.
4. *Quality assurance and control (QA/QC)*: QA/QC can be improved by:
 - a. Determining likely differences in the air sampling results depending on the method used (e.g. depending on the air sampling equipment used, differences in the orifice diameters and air flow sampling rates could affect aerosol collection efficiencies and effects).
 - b. Setting the minimal spike to two to four times that of the limit of quantitation (LOQ; cf. AEATF II 2009b: 42, 46).
 - c. Considering other variables that may influence the measurement of exposure, including whether the surface being treated is dry or wet at the time of the next spray application and whether the applicant accidentally wiped the surface after spraying. The protocol should indicate that there will be a maximum of two workers on any given day in the same location.

Ethics

Charge to the Board

If the proposed AEATF II aerosol application scenario and field study protocol AEA04 is revised as suggested in EPA's review and if the research is performed as described: Is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

Board response to the Charge

The Board concluded that the protocol submitted for review, if modified in accordance with EPA (Leighton, Walls and Sherman 2009) and HSRB recommendations, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L.

HSRB Detailed Recommendations and Rationale

This is a protocol for third-party research involving intentional exposure of human participants to a pesticide, with the intention of submitting the resulting data to EPA under the pesticide laws (AEATF II 2009a, 2009b, 2009d). Thus, it is subject to the ethical and regulatory

standards of 40 CFR 26, Subparts K and L. The requirements of FIFRA §12(a)(2)(P) relating to informed, voluntary consent and those of the California State EPA Department of Pesticide Regulation study monitoring (California Code of Regulations Title 3, Section 6710) also apply. The protocol was reviewed and approved by an independent human subjects review committee, Independent Investigational Review Board, Inc. of Plantation, Florida, prior to submission (AEATF 2009b, 2009c).

1. Except as noted below, the Board concurred with the conclusions and factual observations of the ethical strengths and weaknesses of the study, as detailed in the EPA's Ethics Review (Leighton, Walls and Sherman 2009). The proposed study is likely to meet the applicable ethical requirements for research involving human participants, in accordance with the following criteria:

- a. *Acceptable risk-benefit ratio.* The risks from participation in the study include: 1) discomfort and heat-related illness from wearing two layers of clothing; 2) discomfort from wearing an air sampling device; 3) reactions from exposure to the test material (including accidental exposure) or to solvents used to obtain residues from hands, face and neck; 4) embarrassment from disrobing in the presence of a research technician; and 5) psychological stress and/or breach of confidentiality for pregnancy test results. These risks are minimized appropriately and are justified by the potential societal benefits, particularly data for new exposure assessments for antimicrobial products applied with pressurized aerosol cans.
 - The surrogate materials consist of a commonly used commercial antimicrobial product, which is known to have low risks. The participants will only be exposed to concentrations of the surrogate compound at accepted exposure thresholds. Candidates who are known to be sensitive to that compound, or who are in poor health, or who have broken skin on their hands, face, or neck will be excluded.
 - Risk of heat-related illness is minimized appropriately. Testing will take place in a temperature-controlled environment, and the heat index monitored with associated stopping rule. There will be a limited time of exposure with rest periods at 30-minute intervals, or more frequently if requested. There also will be close observation of participants, with participants alerted to the signs and symptoms of heat stress.
 - Participants will be reminded about safe handling practices and procedures, wear appropriate personal protective equipment (PPE), and will be monitored for any accidental or unintended product exposure.
 - Minors and pregnant or lactating women are excluded from participation, with pregnancy either confirmed by over-the-counter pregnancy testing on the day of study or by opt-out. The potential stigma resulting from study exclusion due to pregnancy is appropriately minimized.
 - The purpose of the study is to develop more accurate information on worker exposures to liquid antimicrobial products applied using pressured aerosol cans for

indoor surface disinfecting. Although there is no clear benefit to study participation, participants may benefit by requesting their results and using these results to change their working practices. Benefits and risks of participation are clearly articulated in the protocol and informed consent documents.

- Possible participants for this study may be undocumented immigrants. Recruitment materials state that government-issued identification is necessary for enrollment in this study.
- A valid government-issued form of identification is necessary for enrollment. Volunteers who lack proper identification are excluded from study participation but no other action is taken, minimizing any social risks to undocumented workers from disclosure of their status to law-enforcement or immigration authorities.

b. *Voluntary and informed consent of all participants*

- The informed consent documents clearly state that study participants can withdraw at any time without penalty.
- The Board disagrees with the EPA comment that “no potential subjects are from a vulnerable population” (Leighton, Walls and Sherman 2009: 11). In fact, participants in this study might represent particularly vulnerable populations and thus be susceptible to coercion or undue influence. Some participants may be educationally or economically disadvantaged, or may not be native speakers of English. However, the risk of coercion or undue influence is appropriately minimized as follows:
 - Monetary compensation is roughly equivalent to the average daily wage of janitorial workers in Fresno, California, and so is not so high as to unduly influence participants.
 - Spanish translations of all informed consent documents, informational packets, and recruitment flyers are available. If necessary, the informed consent process will be conducted in Spanish by a member of the research team fluent in that language.
 - The participants communicate directly with the researchers about their interest in enrolling in the study. Recruitment is not conducted through employers.

c. *Equitable selection of study participants*

- The study is designed to recruit an appropriately diverse population of participants who represent professional janitorial workers in the Fresno County area. The researchers plan to place recruitment notices in three newspapers that cater to the general population, the African-American population, and the Latino population.

2. The Board recommended that the study protocol be modified to address the few concerns noted in the EPA's Ethics Review (Leighton, Walls and Sherman 2009). The Board also made the following additional recommendations:
- The Board recommended that the consent form be reviewed to make sure that it is at an appropriate reading level for the proposed participant population. In some instances, there appear to be word choices that could be simplified (e.g., wording such as "non-porous surfaces", "pressurized aerosol can" instead of "spray can", and assuming that the volunteer knows what a Material Safety Data Sheet is).
 - The Board agrees with the EPA ethics review that the informed consent form should read, "We will pay for needed medical treatment that is not paid for by your own insurance of a third party under which you are covered."
 - As some possible participants for this study may be undocumented immigrants, recruitment materials should more explicitly state that a valid government-issued form of identification is necessary for enrollment.
 - The Board recommended that the Task Force ensure that documents in Spanish are reviewed by someone familiar with the dialects written and spoken in the target community. The National Standards for Culturally and Linguistically Appropriate Services in Health developed by the Department of Health and Human Services, the Office of Minority Health has stressed the importance of treating medical patients in a "culturally and linguistically appropriate manner" (Office of Minority Health 2001, 3). The same respect should be extended to participants in EPA- or third party-conducted research, with materials such as informed consent forms and recruitment flyers written in ways that reflect "the dialectic and cultural nuances as well as the acculturation, educational, and literacy levels of the local target population" (Office of Minority Health 2001, 80).
 - The protocol provides for use of a community notification flyer. However, one neglected community includes persons who might be staying in the hotels where the study is conducted. The flyer should be revised so that it communicates the goals of the study and risks to that group. These flyers should also be posted in locations so that hotel guests are likely to see it. Alternatively, the researchers should consider conducting the research in areas away from hotel guests.
 - The exclusion criteria should be revised to eliminate some groups that might be at higher risk of physical harm but are not presently excluded. This might include participants who might be immunosuppressed for a variety of reasons, those with severe diabetes, and those with other conditions that pose a health risk.

REFERENCES

- Antimicrobial Exposure Assessment Task Force II (AEATF II). 2009a. AEATF II Aerosol Study Vol. 1 Primary Documentation: Aerosol Application Scenario Design. Dated August 4, 2009. Unpublished protocol prepared by the AEATF II.
- Antimicrobial Exposure Assessment Task Force II (AEATF II). 2009b. AEATF II Aerosol Study Vol. 2 Primary Documentation: Study Protocol and IIRB Approval and Documentation. Dated August 4, 2009. Unpublished protocol and documentation prepared by the AEATF II.
- Antimicrobial Exposure Assessment Task Force II (AEATF II). 2009c. AEATF II Aerosol Study Vol. 3 Primary Documentation: IIRB Communications. Dated August 4, 2009. Unpublished documentation prepared by the AEATF II.
- Antimicrobial Exposure Assessment Task Force II (AEATF II). 2009d. AEATF II Aerosol Study Vol. 4 Standard Operating Procedures for a Multi-Year Antimicrobial Chemical Exposure Monitoring Program. Dated August 4, 2009. Unpublished documentation prepared by the AEATF II.
- Carroll, S. 2009a. Efficacy Test of KBR3023 (Picaridin; Icaridin)-Based Personal Insect Repellents (20% Cream and 20% Spray) with Ticks under Laboratory Conditions. Dated July 30, 2009. Unpublished protocol prepared by Carroll-Loye Biological Research. MRID 47836801.
- Carroll, S. 2009b. Carroll-Loye Study LNX-003 Proposed Amended Language. Dated September 18, 2009. Unpublished protocol amendment prepared by Carroll-Loye Biological Research.
- EPA HSRB. 2006a. June 27-30, 2006 EPA Human Studies Review Board Meeting Report.
- EPA Human Studies Review Board. 2006b. October 18-19, 2006 Human Studies Review Board Meeting Report.
- EPA Office of Pesticide Programs. 2009. A Review of the Relationship between Pyrethrins, Pyrethroid Exposure and Asthma and Allergies. Revised September 2009. Unpublished document prepared by the by Office of Pesticide Programs, United States Environmental Protection Agency.
- Independent Institutional Review Board, Inc. (IIRB, Inc.). 2009. Supplemental IIRB, Inc., Documentation Package. Unpublished materials prepared by IIRB.
- Leighton, T., C. Walls and K. Sherman. 2009. Science and Ethics Review of AEATF II Aerosol Scenario Design and Protocol for Exposure Monitoring. Dated September 21, 2009. Unpublished document prepared by Office of Pesticide Programs, United States Environmental Protection Agency.

Lisi, P. 1992. Sensitization Risk of Pyrethroid Insecticides. *Contact Dermatitis* 26:349-350. MRID 47852801.

Newton, J.G. and A.B. Breslin. 1983. Asthmatic Reactions to a Commonly Used Aerosol Insect Killer. *Medical Journal of Australia* 1:378-380. MRID 47686201.

Office of Minority Health, Department of Health and Human Services. 2001. National Standards for Culturally and Linguistically Appropriate Services in Health Care: Final Report. Washington, DC: U.S. Department of Health and Human Services.

Sherman, K. 2009a. Ethics Review of Pre-Rule Intentional Exposure Human Toxicity Study (Newton and Breslin 1983). Dated September 16, 2009. Unpublished document prepared by Office of Pesticide Programs, United States Environmental Protection Agency.

Sherman, K. 2009b. Ethics Review of Pre-Rule Intentional Exposure Human Toxicity Study (Lisi 1992). Dated September 16, 2009. Unpublished document prepared by Office of Pesticide Programs, United States Environmental Protection Agency.

Sherman, K., and K. Sweeney. 2009. Science and Ethics Review of Protocol for Human Study of Tick Repellent Performance. Dated September 21, 2009. Unpublished document prepared by Office of Pesticide Programs, United States Environmental Protection Agency.